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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 36

Serial Number: 09/091,561
Filing Date: 8/21/98
Appellant(s): Plouet et al.

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JUL 15 2003
GROUP 2800

Philip A. DuBois
For Appellant

EXAMINER'S ANSWER

This is in response to Appellant's brief on appeal filed 1/21/03.

(1) Real Party of Interest.

A statement identifying the real party of interest is contained in the brief.

(2) Related Appeals and Interferences Identified.

A statement identifying that no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims.

The statement of the status of claims contained in the Brief is correct.

(4) Status of Amendments After Final.

The Appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) **Summary of Invention.**

The summary of invention contained in the brief is deficient for the following reasons. The instant claims are drawn to a specific type of antibody, i.e., an anti-idiotypic antibody. Appellant's summary fails to adequately describe just what an anti-idiotypic antibody is. Appellant states that an anti-idiotypic antibody is "a second generation antibody ... an antibody raised to an antibody," and cites page 8, lines 3-21. Said definition is rather unscientific and somewhat misleading. Additionally, the specification at page 8, lines 3-21 merely discloses how said antibody is assertedly made. An anti-idiotypic antibody is actually an antibody in which the antibody binding sites comprise something akin to mirror images of the binding sites of the antibody to which it is raised. More specifically, an anti-idiotypic antibody acts as a ligand for the original antibody. In the instant application VEGF is a ligand for the flt and flk(KDR) receptors. An antibody was raised to VEGF; said antibody then had the receptor-binding capability of flt or flk, i.e., it bound VEGF. A second "anti-idiotypic" antibody was raised to the antibody binding site of the anti-VEGF antibody. This second anti-idiotypic antibody then would be expected to possess the capability of binding the flt or flk receptor as does VEGF. In the instant case VEGF binds both flt and flk, however, the anti-idiotypic antibody of the instant claims binds flk but not flt.

Appellant follows with a discussion of the asserted value of the invention that is inappropriate in the summary, i.e., "In the present invention, Appellants demonstrate that it is possible to produce anti-idiotypic antibodies that are capable of treating pathologies involved in angiogenesis and neovascularization." It must be noted, however, that no such capabilities are disclosed.

Appellant then asserts that at page 3, lines 1-23, the specification discloses that Fab fragments of the anti-idiotypic antibody of the instant claims can "block VEGF from binding to KDR and flk-1 and inhibit the proliferation of endothelial cells." Said assertion is factually incorrect; the cited passage is silent regarding Fab fragments and additionally, said passage discloses that an anti-idiotypic antibody would stimulate the KDR receptor (lines 11-12).

(6) Issues.

The Appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims.

The Appellant's statement in the brief that certain claims do not stand or fall together is not agreed with. The Appellant states that because the Fab fragments of the claims are addressed separately from the antibodies of the claims, they are independently patentable. The Fab fragments of Claims 27, 28, and 34 are not patentably distinct from the antibody of Claims 25, 26, 29, 30, 32, 33, and 35 because they are merely antigen binding fragments of said antibodies. Antigen binding fragments are not considered to be patentably distinct from the antibodies from which they are derived.

(8) Claims Appealed.

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record.

No prior art is relied upon by the examiner in the rejection of the claims under appeal.

(10) Grounds of Rejection.

The following ground(s) of rejection are applicable to the appealed claims:

Claims 25-30 and 32-35 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation because if one of skill in the art performed the method disclosed in the specification said method would not result in the product of the instant claims.

The method set forth in the specification would result in a polyclonal antiserum. It is clear however, that only a monoclonal antibody can function in the intended capacity of the

antibody of the instant claims. A polyclonal antiserum (from which the polyclonal antibody of the specification would be derived) would be expected to comprise a mixture of antibodies, some would bind flk-1, some would bind flt, and some would bind both. Such is the nature of a polyclonal antibody (note that the term "polyclonal antibody" is used; the term actually encompasses a collection of different antibodies that bind different epitopes on the same ligand). Said polyclonal antibody then could not meet the limitations of the claims. Accordingly, only the rare monoclonal antibody, which would comprise a single binding specificity for flk-1 but not flt, would meet the limitations of the claims. This concept is demonstrated in Inventor Plouet's declaration, filed 9/11/00, which indicates that in one experiment, 3 of 4 of the monoclonal antibodies produced after a polyclonal response were not specific for flk-1 (see results, page 5). Because the specification fails to disclose that the claimed antibody must be a monoclonal antibody, and because the specification fails to disclose how to produce and isolate said antibody, the specification fails to teach one of skill in the art how to make the invention of the instant claims.

Additionally, regarding Fab fragments, at page 8 in Inventor Plouet's declaration, filed 9/11/00, the Declarant states, "Fab fragments, which are monovalent, exert an opposite function in endothelial cells: they can only block the VEGF receptors and, in no case, can induce a function similar to that exerted by the anti-idiotypic antibody, namely, receptor dimerization, internalization and cell proliferation." Clearly then, with regards to the Fab fragments of the claims, the specification fails to teach one of skill in the art both how to make the invention of the instant claims and how to use the invention of the instant claims.

(11) Response to Argument

Appellant argues that the instant rejection does not merit affirmation for three reasons. First, the present specification clearly enables one skilled in the art to make and use the claimed antibody. Second, one of ordinary skill in the art would readily be able to make monoclonal antibodies according to the invention, given the teaching of the purified polyclonal fraction in the present specification. And third, the present specification clearly enables one skilled in the art to produce or use Fab fragments of the claimed invention.

Regarding an enabling disclosure, the Appellant argues "The claimed invention is directed to anti-idiotypic VEGF antibodies. The claims do not limit the antibody to a polyclonal or a monoclonal antibody."

Appellant's statement is true in that the specification fails to even disclose the term monoclonal antibody. However, the method disclosed in the specification would result in a polyclonal antiserum which would not meet the limitations of the claimed antibody or result in an antibody that would be enabled for it's intended use.

Appellant argues "In present disclosure, the polyclonal antiserum is further purified to the Ig2 J fraction ... Although the fraction may include some anti-idiotypic antibodies that bind to both flk and flt, that fraction also clearly contains the Ig2 J claimed antibody."

By Appellant's own admission then, the antibody of the instant claims has not actually been isolated by the methods set forth in the specification. The Ig2 J fraction set forth in the specification comprises merely an affinity purified fraction that would again include antibodies that bind flk, flt, or both. This fact is confirmed in the 1.132 declaration of Inventor Plouet submitted 3/25/02. The Inventor further stated that only 15 to 20% of immunized rabbits would produce the claimed antibody. Clearly then, further isolation (that would be accomplished by creating a monoclonal antibody, further isolation that is not disclosed in the specification) is key in meeting even the most basic limitation of the claims, i.e., an antibody that binds flk and not flk. Unless the claimed antibody is separated from the other antibodies in the polyclonal antiserum, the claims are akin to claims reciting the blue paint in a bucket of green paint.

Regarding Appellant's second point, that one of ordinary skill in the art would readily be able to make monoclonal antibodies according to the invention, given the teaching of the purified polyclonal fraction in the present specification, Appellant argues "one of ordinary skill in the art would already possess the requisite skills and knowledge to conduct the further protocols, screening and isolation steps to that end."

Again, the Appellant has conceded that the specification does not teach how to make the invention of the claims, instead Appellant now argues that the additional steps required would be routine. First it must be noted that the specification does not instruct the skilled practitioner to perform *any* additional

steps. Said instruction has only come in the form of arguments and declarations post-filing. Indeed, until the submission of Inventor Plouet's declaration on 9/11/00, Appellant's maintained that the specification itself was enabling, i.e., that the method disclosed in the specification would result in the claimed product. As this is clearly not the case, Appellant submitted several additional declarations indicating that monoclonal antibody production is routine. As set forth in *Kawai v. Metlesics*, 480 F.2d 880, 178 USPQ 158 (CCPA 1973) the invention is that which is disclosed in the specification at the time of filing, i.e., the *specification* itself must provide the invention's enablement. While the decision involved the utility requirement it also stated:

> "We also think that proof of a constructive reduction to practice would also require that there be sufficient disclosure in the specification to enable any person skilled in the art to take advantage of that utility where it would not be obvious how this is done. This latter requirement is, of course, the so-called "how to use" requirement of section 112. It goes without saying that proof of a constructive reduction to practice would also require that the specification be sufficient to enable anyone skilled in the art to make the invention, i.e., the "how to make" requirement of section 112 should also be met by the specification."

In the instant application, the specification simply fails to adequately disclose to the skilled practitioner how to make the claimed invention. Appellant's post-filing submissions cannot remedy the shortcoming.

Appellant argues "Appellants believe that the Examiner fails to meet his burden in showing that the claimed invention is not supported by an enabling disclosure ... Moreover, it is noted that the Examiner fails to provide any evidence contesting the statements made in the declaration attesting to the enablement of the claimed invention."

It remains the Examiner's position that the specification fails to teach how to make the claimed invention because the method of the specification would not result in an antibody that meets the limitations of the claims or result in an antibody that would be enabled for it's intended use. Said position was confirmed by Inventor Plouet in has 1.132 declaration of 3/25/02.

Appellant reviews the additional steps that would be required to produce the antibody of the instant claims, i.e., immunization, screening, monoclonal antibody production, etc. Appellant reiterates the argument that said additional steps would be routine. Appellant concludes the section "Thus, Appellants submit that additional process steps not recited in the present disclosure would be well known to one of ordinary skill in the art and reflect conventional hybridoma techniques."

It remains the Examiner's position that, while the specification need not disclose the methodology of performing routine steps, it must at minimum direct the skilled artisan to perform those routine tasks (such as producing a monoclonal antibody) that are necessary to make the claimed product. After-the-fact direction cannot take the place of an enabling specification.

Regarding Appellant's third point, "The present specification clearly enables one skilled in the art to produce or use Fab fragments of the claimed invention," Appellant argues "Appellants agree with the Examiner in that the Fab fragments of the present invention do not exert the same functional activities of an antibody such as dimerization, internalization and self-proliferation. However, the claims do not recite these functions."

Appellant's assertion is incorrect as it regards Claim 28 which depends on Claim 26 (which recites the functional limitations). While Claims 27 and 34 may not recite the functional limitations, an invention must be enabled for it's intended use. In the instant case the intended use requires the functional limitations, i.e., "The invention relates to the use of anti-idiotypic vascular endothelial growth factor antibodies for the preparation of a medicament for treatment of pathologies involving endothelial cells engaged in an angiogenesis process, to promote the angiogenesis, without affecting quiescent endothelial cells," (page 4 of the specification). Accordingly, while not present in all claims, the functional limitations of the specification (and Claim 26) must still be met by the Fab fragment of the claims to be enabled for it's intended use.

Regarding how to make said fragment, as the specification is deficient in disclosing how to make the antibody of the independent claims, it is also deficient in disclosing how to make the Fab fragment of the claims because the Fab fragment is merely an enzymatic cleavage product of the antibody. Accordingly, as regards the Fab fragment of Claims 27, 28, and

34, the specification fails in teaching both how to make and how to use the claimed invention.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Primary Examiner
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July 3, 2003

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